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The BRICS (Bronchiectasis Radiologically Indexed CT Score)- a multi-center study score for use in idiopathic and post infective bronchiectasis

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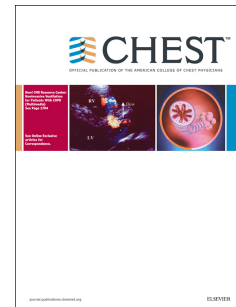
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The BRICS (Bronchiectasis Radiologically Indexed CT Score)- a multi-center study score for use in idiopathic and post infective bronchiectasis

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Running head: BRICS in bronchiectasis
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PS, PV and MKC: collecting data and writing the manuscript.

AGR: writing the manuscript.

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Conflicts of Interest: JJ has received consultant fees from Boehringer Ingelheim. MH has received speaking fees from Vertex Pharmaceuticals. All others declare no conflicts of interest.

ABSTRACT

Objectives

The aim of our study was to develop a simplified radiological score that could assess clinical disease severity in bronchiectasis.

Methods

The BRICS (**Bronchiectasis Radiologically Indexed CT Score**) was devised based on multivariable analysis of the Bhalla score and their ability in predicting clinical parameters of severity. The score was then externally validated in 6 centers in 302 patients.

Result

184 HRCT scans were scored for the validation cohort. In a multiple logistic regression model, disease severity markers significantly associated with the Bhalla score were percentage predicted FEV₁, sputum purulence and exacerbations requiring hospital admission. Components of the Bhalla score that were significantly associated with the disease severity markers were bronchial dilatation and number of bronchopulmonary segments with emphysema. The BRICS was developed with these two parameters. The receiver operator curve values for BRICS in the derivation cohort were 0.79 for percentage predicted FEV₁, 0.71 for sputum purulence and 0.75 for hospital admissions/year; and 0.81, 0.70 and 0.70 respectively in the validation cohort. Sputum free neutrophil elastase was significantly elevated in the group with emphysema on CT.

Conclusion

A simplified CT scoring system can be used as an adjunct to clinical parameters to predict disease severity in patients with idiopathic and post-infective bronchiectasis.

TEXT**INTRODUCTION**

High resolution CT scan of the thorax (HRCT) remains the imaging gold standard for diagnosing bronchiectasis and for diagnosis patients should have bronchial dilatation at least greater than the adjacent pulmonary artery [1-5]. In 1991, Bhalla *et al* published a detailed scoring system to quantify structural lung abnormalities in patients with cystic fibrosis using thin section CT scans [6]. Subsequent to that, Reiff *et al* developed a scoring system that described the site, type and extent of bronchiectasis and since then 'the modified Reiff score' is frequently used in studies [7]. The Bronchiectasis Severity Index and FACED score were devised using several clinical parameters including number of lobes affected by bronchiectasis on CT scan, to predict severity and prognosis in bronchiectasis [8,9]. However, both studies included a heterogeneous population of bronchiectasis with a variable smoking history. Additionally, the radiology scoring in both scores only took into account the number of lobes affected by bronchiectasis [9] and the presence of cystic bronchiectasis [8]. Both these scores are easy to use but are multidimensional.

Hence, the role of CT imaging in defining bronchiectasis phenotypes above and beyond conventional characterization remains to be fully determined. CT scanning as a phenotypical marker of airway disease is yet to be established and no studies have stratified for the etiology of bronchiectasis [10].

The aim of our study was to develop a simple CT score that could assess clinical disease severity in idiopathic and post infective bronchiectasis in a cohort with limited smoking history, using multivariable models.

METHODS

Study design

A prospective study was carried out between 2006 and 2013, at the Royal Infirmary of Edinburgh, United Kingdom. All new adult patients attending the bronchiectasis clinic routinely had a non contrast HRCT acquired with 1mm slices as a single breath hold on a 64 multi-slice CT scanner (Toshiba Medical Systems, Tokyo Japan). Clinical parameters recorded at the time of the CT scan were: spirometry; degree of sputum purulence (muroid =1, mucopurulent =2 and purulent ≥ 3) [11]; qualitative sputum microbiology (baseline, 6 and 12 months following); exacerbations requiring antibiotics and hospital admissions for bronchiectasis exacerbations in the following year. Neutrophil elastase was measured in sputum when available.

Ethical approval

Caldicott approval was given for conducting the study.

Imaging

Across all centers, CT scans were obtained using a 64-slice multiple detector CT scanner (Toshiba/ Seimens/ Phillips) or a 4-slice multiple detector CT scanner (Toshiba/ Seimens/ Phillips). All scans were reconstructed using a high spatial frequency, B70 kernel. All patients were scanned from lung apices to bases, supine, at full inspiration, with 1.0mm section thicknesses at either 1mm or 10mm intervals using a peak voltage of 120kVp with tube current modulation (range 30-140mA). Images were viewed at window settings optimized for the assessment of the lung parenchyma (width 1500 Hounsfield Units (H.U.); level -500 H.U.).

Across centers, all images were reviewed by a consultant radiologist with experience of reporting HRCT and a consultant respiratory physician with a major interest in bronchiectasis. A consensus score was produced using the criteria outlined below.

Bronchiectasis was present when one or more of the criteria were fulfilled: (1) internal diameter of the bronchus greater than that of the adjacent pulmonary artery; (2) a lack of tapering of the bronchial lumen towards the periphery.

In the derivation cohort, CT scans were scored independently and a kappa coefficient was calculated.

Patients (derivation and validation cohort)

Inclusion criteria: Patients having a clinical diagnosis of bronchiectasis with regular cough and sputum production with or without recurrent chest infections and cause of bronchiectasis being idiopathic or post infective as per British Thoracic Society guidelines [10]. Exclusion criteria: Alpha 1 anti trypsin deficiency, smoking history of more than 5 pack years, current smoker or ex-smoker <1 year.

Scoring the CT scans

Bhalla and modified Reiff scores were calculated on all patients that met inclusion and exclusion criteria. Both of these scores were jointly carried out by consensus by a chest physician and radiologist both blinded to the clinical status of the patient. The Bhalla score was calculated by scoring each of the 9 categories and then adding up the total score [6]. The total points were then subtracted from 25 to obtain the Bhalla score. The maximum points that can be obtained in a Bhalla score is 22 (prior to subtracting from 25; Appendix 1).

The modified Reiff score [7] used (0-18) was based on the number of lobes (maximum 6 including lingula) and the severity of bronchial dilatation in comparison to the adjacent vessel (0=no bronchiectasis; 1= 1-2 times; 2= 2-3 times; 3= greater than three times).

Subdivision of the CT Scores

The total range for the Bhalla score is from 3-25, where a lower score indicates more severe radiological bronchiectasis. This score was subdivided into mild (16-25), moderate (9-15) and severe (3-8).

The total range of the Modified Reiff Score is from 0-18. This was subdivided into mild (1-6); moderate (7-12) and severe (13-18).

BRICS

The BRICS (**Bronchiectasis Radiologically Indexed CT Score**) score (detailed in the results section) would be devised based on multivariable analysis of the Bhalla score and their ability in predicting clinical parameters of severity.

External validation of the BRICS

The BRICS was externally validated by 6 centers across the UK and Europe- by a chest physician and a radiologist. The score was validated in 50 consecutive individual patients from each center (except Dundee and London, UK- where the score was validated in 60 and 42 patients respectively). The protocols for imaging was similar to our center, and was viewed in the respective PACS version available at various centers.

Sputum neutrophil elastase

Sputum neutrophil elastase was measured when available in the derivation cohort. Sputum was ultracentrifuged at 50000 g for 90 min at 4°C. The colloidal solution phase was stored at -70°C until needed for analysis of the activity of free neutrophil elastase. We measured free elastase activity by spectrophotometry with a synthetic substrate (methoxysuccinyl-Ala-Ala-Pro-Val paranitroanilide; Sigma, Gillingham, UK) [14-16].

BSI and FACED score

The BSI (Bronchiectasis Severity Index) and the FACED [10] score were calculated on all patients in the derivation and validation cohort (except in London cohort). In the BSI score- a score between 0-4 indicated mild disease, 5-8 moderate and 9 or over severe disease. In the FACED score- a score between 0-2 indicates mild disease, 3-4 moderate disease and 5-7 severe disease.

STATISTICAL ANALYSIS

Statistical analysis was performed using graph pad PRISM, version 5 (GraphPad Software; San Diego, California). Parametric and non-parametric data are presented as mean (standard error of mean-SEM) and median (interquartile range- IQR).

Adjustment for potential confounders was achieved using multivariable logistic regression. Multivariable regression models were constructed by including demographic (age, gender, co-morbidities, smoking history—as listed in Table 1) and clinical characteristics (FEV₁ >80% predicted, FEV₁ 50-80% predicted, FEV₁ <50% predicted, colonization with *Pseudomonas aeruginosa* and/or enteric gram negative organisms, colonization with other potential pathogenic organisms, sputum purulence, bronchiectasis exacerbations, hospital admissions for bronchiectasis exacerbations) to assess independent clinical factors that predict a severe Bhalla score; with the Bhalla score as the dependent variable. Following this, a logistic regression was performed to assess independent factors from the Bhalla score that predicted clinical disease severity. ROC analyses of all three scores (Bhalla, modified Reiff and BRICS) to the clinical severity markers were done. One-way ANOVA (with Bonferroni's correction for multiple comparisons) was used to compare the mild, moderate and severe sub-scores of the Bhalla, modified Reiff score and the BRICS to each of the severity parameters. A Mann Whitney U and chi square analysis was done to compare the free neutrophil elastase in the derivation cohort.

A one-way ANOVA (with Bonferroni's correction for multiple comparisons) and ROC analysis of the collated independent data was done to validate BRICS externally.

RESULTS

184 consecutive CT scans of patients with idiopathic or post infective etiology, were analyzed in the derivative cohort. Baseline characteristics of the study patients in all the cohorts, including the validation cohorts are shown in Table 1.

	Edinburgh	Dundee	London	Italy	Belgium	Spain	Cambridge
N	184	60	42	50	50	50	50
Age	65 (57-72)	70.5 (65-76)	67 (58-73)	67 (67-73)	61 (44-71)	66.5 (51-77)	62 (48-73)
Gender (Female %)	59%	63%	76%	68%	76%	84%	68%
Etiology							
Idiopathic	92 (50%)	44 (73.3%)	16 (38%)	17 (34%)	31 (62%)	38 (76%)	14 (28%)
Post infective	92 (50%)	16 (26.7%)	26 (62%)	33 (66%)	19 (38%)	12 (24%)	36 (72%)
Chronic Colonization*	116 (63%)	32 (53.3%)	25 (59.5%)	36 (72%)	10 (20%)	13 (26%)	20 (40%)
Colonization with <i>P. aeruginosa</i>	50 (43%)	5 (8.3%)	17 (40.4%)	15 (30%)	6 (12%)	9 (18%)	12 (24%)
Comorbidities							
IHD	6 (3%)	10 (16.7%)	1 (2.3%)	2 (4%)	2 (4%)	3 (6%)	3 (6%)
Previous malignancy	6 (3%)	4 (6.7%)	0	6 (12%)	3 (6%)	6 (12%)	6 (12%)
ICS	132 (72%)	30 (50%)	26 (62%)	19 (38%)	33 (66%)	38 (76%)	40 (80%)
FEV₁ (L)	1.85 (1.36-2.4)	1.83 (1.3-2.4)	1.5 (1.1- 1.9)	1.8 (1.1- 2.4)	2 (1.4-2.5)	1.8 (1.1- 2.3)	1.9 (1.4-2.7)
% predicted FEV₁	77% (61-95%)	83% (58- 104)	66% (47-80)	88% (69- 101)	77% (62- 90)	76% (54-97)	80% (69-94)

Table 1. Baseline characteristics of the derivation cohort and independent cohorts

*chronic colonization defined as isolation of pathogenic organism at least two times when clinically stable in the year following CT scanning; Pathogens can up to more than 100% in view that there can be combined pathogens or different pathogens isolated at different time points; ICS= inhaled corticosteroid; IHD= ischemic heart disease; FEV₁= Forced expiratory volume in 1 second.

Intra class coefficient

The kappa coefficient between the chest physician and chest radiologist was 0.88 (95% CI 0.82-0.94).

Clinical severity markers associated with the Bhalla score (Table 2)

In a logistic regression model, factors significantly associated with the Bhalla score were FEV₁ <50% predicted, sputum purulence and hospital admissions.

	Estimate	Std. Err.	Z-Stat	P-Value
Gender (male)	-0.1	0.5	<-1	0.8
Age>65 years	-0.3	0.5	<-1	0.5
FEV₁ 50-80% predicted	-0.6	1.1	<-1	0.5
FEV₁<50% predicted	-2.5	0.6	-4	<0.0001
Purulent sputum	-1.0	0.5	-2	0.04
Chronic colonization	-1.4	0.8	-2	0.08
Chronic colonization with <i>P.aeruginosa</i> ± enteric gram negative organism	0.7	0.8	<1	0.4
Colonization with other PPMs	1.4	0.7	2	0.06
Hospital admission	-2.2	0.6	-3.5	0.0006
≥ 3 exacerbations/ year	0.5	0.5	1	0.3

Table 2. Logistic regressions using Bhalla score with severity parameters. FEV₁= Forced expiratory volume in 1 second; PPM= potential pathogenic microorganisms.

Factors of the Bhalla score associated with clinical severity parameters

The three clinical disease severity markers associated with the Bhalla score were $FEV_1 < 50\%$ predicted, sputum purulence and hospital admissions (Table 2). Of the 9 components of the Bhalla score (Appendix 1), only the degree of bronchial dilatation and number of bronchopulmonary segments with emphysema were independently associated with $FEV_1 < 50\%$ predicted, sputum purulence and hospital admissions (see Table 3), by logistic regression analysis. Emphysema was diagnosed by assessing the lung parenchyma on lung windows and classified as para-septal, centrilobular or panacinar based on the accepted morphological diagnostic criteria [12].

Variable	P value
Dependent variable: $FEV_1 < 50\%$	
Bronchial dilatation	0.04
Dependent variable: Hospital admissions	
Number of bronchopulmonary segments with emphysema	0.02
Dependent variable: Sputum purulence	
Number of bronchopulmonary segments with emphysema	0.03

Table 3. Logistic regression of the Bhalla score.

Simplified scoring system

The BRICS (**B**ronchiectasis **R**adiologically **I**ndexed **C**T **S**core) was developed by combining the parameters of bronchial dilatation and number of bronchopulmonary segments with emphysema, as these two components of the Bhalla score were significantly associated with clinical severity markers. The new score ranges from 0 to 5, where 1 indicates mild disease, 2-3 indicates moderate disease and >3 indicates severe disease (Table 4).

Score	0	1	2	3
Bronchial dilatation	Absent	Mild (lumen just > diameter of adjacent vessel)	Moderate (lumen 2-3 times > diameter of adjacent vessel)	Severe (lumen >3 times diameter of adjacent vessel)
Number of bronchopulmonary segments with emphysema	Absent	1-5	>5	

Table 4. BRICS derived from combining bronchial dilatation with number of bronchopulmonary segments with emphysema.

ROC analysis of individual radiology scores to clinical severity parameters

The receiver operator curves of the Bhalla, modified Reiff and the BRICS in predicting the clinical severity parameters- percent predicted FEV₁, sputum purulence and hospital admissions were calculated. The ROC values for the Bhalla score were 0.89 for percentage predicted FEV₁, 0.70 for sputum purulence and 0.62 for hospital admissions per year. The ROC values for the modified Reiff score were 0.58 for percentage predicted FEV₁, 0.75 for sputum purulence and 0.57 for hospital admissions per year. The ROC values for the BRICS were 0.79 for percentage predicted FEV₁, 0.71 for sputum purulence and 0.75 for hospital admissions per year.

Comparison of the BRICS to the BSI and FACED score

The ROC values for BSI were 0.58 for percentage predicted FEV₁, 0.54 for sputum purulence and 0.61 for hospital admissions per year. The ROC values for the FACED score were 0.53 for percentage predicted FEV₁, 0.63 for sputum purulence and 0.55 for hospital admissions per year.

BRICS correlates with clinical disease severity markers (Figure 1)

The Bhalla ($p<0.0001$) and the BRICS ($p=0.004$) are significantly related to percentage predicted FEV₁. The modified Reiff score ($p<0.0001$) and the BRICS ($p=0.008$) are significantly related to the sputum purulence. The Bhalla score ($p=0.005$) and the BRICS ($p=0.0001$) are significantly related to hospital admissions per year. The BRICS is significantly related to all three clinical disease severity markers.

Free neutrophil elastase

Sputum was available in 113 patients of the derivation cohort. Of these, 22 (19%) had emphysema on their CT scans and 91 (81%) did not. The mean (SEM) elastase in the group that had emphysema on the CT scan was 60.6 ng/ml (± 13.7) and in the other group was 7.6 ng/ml (± 1.6), $p<0.0001$ (figure 2).

Validation of the BRICS in independent cohorts

The baseline characteristics of the independent cohorts are described in table 1. The data from the independent cohorts was collated and the BRICS calculated. Cumulatively, percent predicted FEV₁ ($p<0.0001$), sputum purulence ($p=0.0007$) and hospital admissions ($p<0.0001$) were all significantly related to the BRICS (figure 3). The ROC curve value for percent predicted FEV₁ was 0.81, for sputum purulence 0.70 and hospital admissions 0.70. The results were similar in each validation center.

BRICS severity compared to severity of BSI and FACED

On combining data from both the derivation and validation cohort, BRICS severity was calculated and the corresponding BSI and FACED scores were tabulated. There was a significant association of the severity of the BRICS to the severity of the BSI and FACED score, $p<0.0001$ for both scores (figure 4).

Emphysema on CT scan

Combining the data from all centers, emphysema was reported in 50% (± 15.6) of the cohort. Data on the type of emphysema was available from 3 centers (Belgium, Edinburgh and London). A total of 48 scans with emphysema sub type were analyzed across these centers. Panacinar emphysema was present in 31 (64%), centrilobular in 9 (19%) and paraseptal in 8 (17%) of the cohort.

DISCUSSION

This is the first multi center international study to develop a radiological scoring system for use in idiopathic or post infective bronchiectasis, in a cohort with limited smoking history. In this study, we developed a simplified scoring system of CT scans in patients with bronchiectasis and found that this score was significantly associated with clinical parameters of disease severity. The BRICS was devised using parameters of bronchial dilatation and number of bronchopulmonary segments with emphysema on HRCT scans of 184 patients in the derivation cohort, with either idiopathic or post infective bronchiectasis. The score ranges from 0 to 5 in this scoring system, where a higher score is indicative of increasing disease severity. The score was significantly associated to percentage predicted FEV₁, sputum purulence and hospital admissions for bronchiectasis exacerbations. In addition, we found that free neutrophil elastase, an established marker of neutrophilic airway inflammation in bronchiectasis [13,14], was significantly higher in the patients who had emphysema on their CT scans. The BRICS was compared to the existing Bhalla score and modified Reiff scores and was found to be as reliable and predictive of disease severity compared to these other scores. This score was then externally validated in a cohort of 302 patients across 6 centers in Europe. The results across these 6 centers were similar and in keeping with the derivation cohort. To the authors' best knowledge this is the first simplified radiological score that has been developed to assess disease severity in patients with idiopathic/post-infective bronchiectasis.

The BSI and FACED score were not significantly associated with percentage predicted FEV₁, sputum purulence and hospital admissions for bronchiectasis exacerbations, but then, these two scores were not designed for the above stated end points. Hence, the BRICS is the first radiological severity score correlating with significantly with clinical parameters that can risk assess for severity.

There are currently no markers to predict radiological disease severity in bronchiectasis. The clinical parameters of severity that were statistically significant in the multiple regression models have been demonstrated to be of significance in previous studies. It is well established that FEV₁ is an important functional marker of pulmonary disease. We have previously demonstrated that sputum purulence is associated with disease severity in bronchiectasis [11]. It seems logical that if a patient requires repeated hospital admissions for bronchiectasis exacerbations as defined by the BTS guidelines [10], it indicates that the patient has more severe disease. In addition, in the Bronchiectasis Severity Index, the authors have demonstrated that prior hospital admissions and FEV₁ <30% predicted are independent predictors of hospital admissions and mortality in bronchiectasis [8].

In this study we were able to demonstrate that the new simplified BRICS can predict disease severity, based on radiological appearances alone. In addition, sub divisions of the BRICS demonstrated that an increasing score is associated with increasing disease severity. Patients with a higher score on the BRICS had lower FEV₁, more purulent sputum and increased hospital admissions for bronchiectasis exacerbations. Validation of the BRICS internationally showed that this was a simple but robust scoring system that can be used in day to day clinical practice.

Free neutrophil elastase was significantly higher in patients with emphysema on CT scan, in the derivation cohort. This is in keeping with data published in the literature [13,14]. Loubeyre *et al* [15] had demonstrated that there was a high prevalence of emphysema in bronchiectasis. Activation of matrix metalloproteinase by free neutrophil elastase has been shown to be one of the mechanisms of driving structural lung damage in early cystic fibrosis [16]. There is evidence to support that unopposed neutrophil elastase activity has come to be implicated in the pathobiology of many lung diseases, particularly in chronic obstructive lung disease. Known for its matrix-degrading capacity and broad substrate repertoire, there is evidence to hypothesize that enhanced neutrophil elastase predominance over its natural inhibitors may result in, or at perhaps intensify, pathologic states such as fibrosis and emphysema [17].

The two components defining the BRICS have been used in studies before. Bronchial dilatation is the classic radiological feature, which defines bronchiectasis on CT scans. Although bronchial dilatation is associated with asthma, chronic bronchitis and pulmonary fibrosis, we can safely confirm that as our study was conducted in a well defined cohort of patients with either idiopathic or post infective bronchiectasis, (which are the two most common causes of bronchiectasis [18]), bronchial dilatation represented bronchiectasis. Loubeyre *et al* demonstrated emphysema in the CT scans of 90 consecutive patients with bronchiectasis and concluded that there was a high prevalence of emphysema in bronchiectasis patients [15].

HRCT is a sensitive non-invasive technique for demonstrating bronchiectasis. The need for the creation of scoring systems comes from the fact that CT as a test depicts structural abnormalities in great detail but is a qualitative image, and the extent of the abnormality has to be quantified as a score in order to be used in statistical analysis [19]. Association studies between CT scans and clinical parameters- mostly lung physiology- have been conducted previously [20,21]. These studies have used the Bhalla score, the modified Reiff score or a simplified score that the authors have agreed upon by consensus. Airflow limitation can be seen in more advanced bronchiectasis [27,28]. Studies have demonstrated that airflow obstruction in bronchiectasis is linked to evidence of structural abnormality on CT scans [9,21,24]. The BRICS and our study findings corroborated with this.

In summary, to the authors' best knowledge, this is the first international multi center simplified scoring system designed for use in idiopathic or post infective bronchiectasis. This is a useful clinical tool to assess radiological and clinical severity in bronchiectasis. This study is not confounded by other etiologies of bronchiectasis and pertains to a cohort with limited smoking history. The significantly higher levels of the neutrophil elastase in the cohort with emphysema on the CT scans compared to those with no emphysema, suggests that elastase is perhaps one of the possible causes for emphysema in this group. There was significant association of the BRICS to the BSI and FACED. The BRICS may be used to follow up patients longitudinally and hence be a useful research tool for future studies. In addition radiological scores could be used as an adjunct to clinical assessment in categorizing patients into disease severity groups, which could then guide management.

LIMITATIONS

This study has been conducted in a cohort where the patients had idiopathic or post infective bronchiectasis. Bronchiectasis due to other etiologies need further study.

CONCLUSION

We have developed and validated a simplified CT scoring system based on degree of bronchial dilatation and number of bronchopulmonary segments with emphysema, in patients with idiopathic and post infective bronchiectasis, with limited smoking history.

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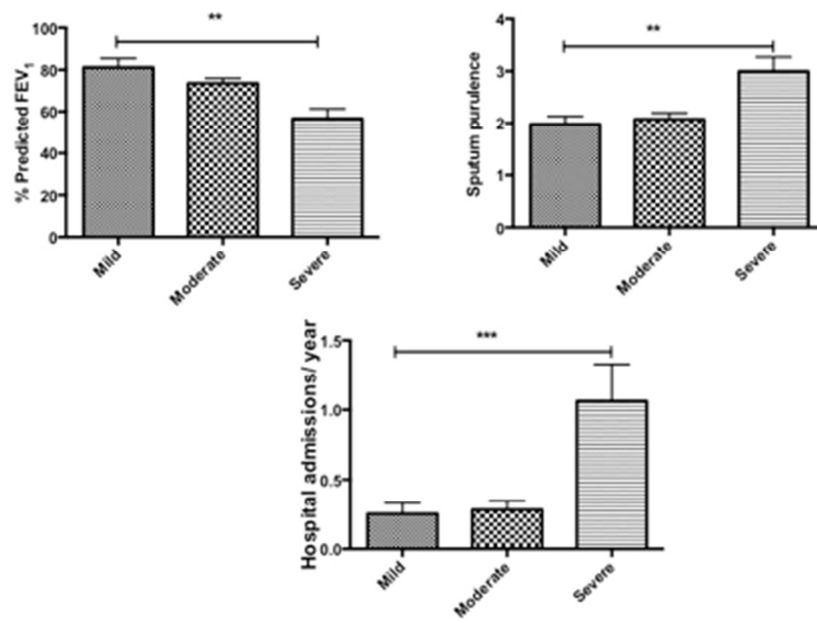
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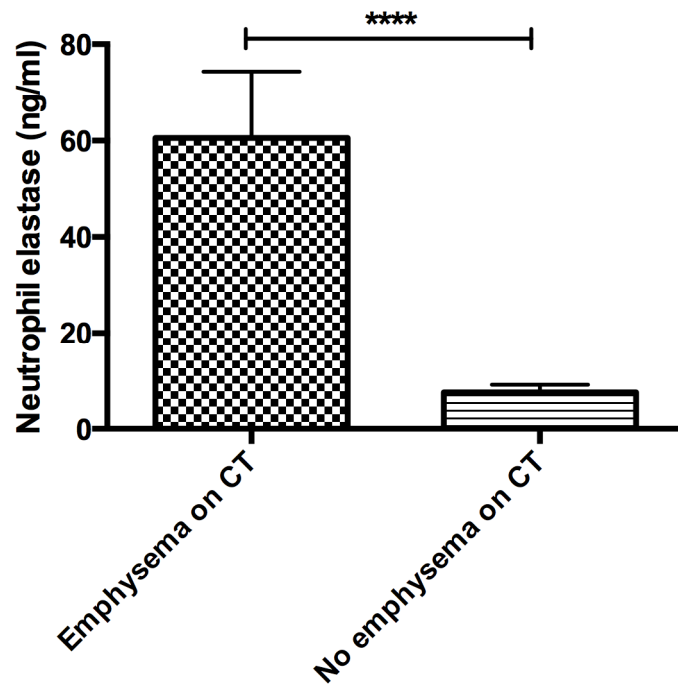
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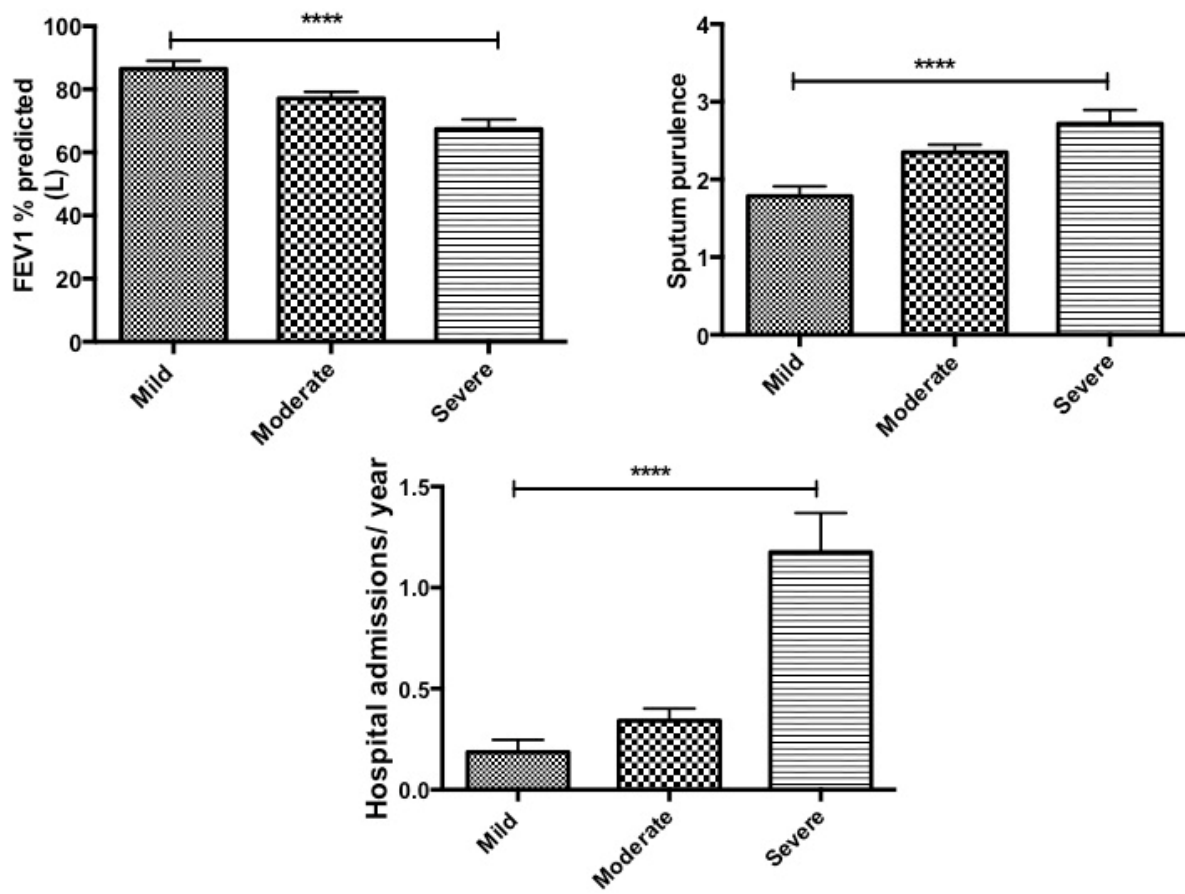
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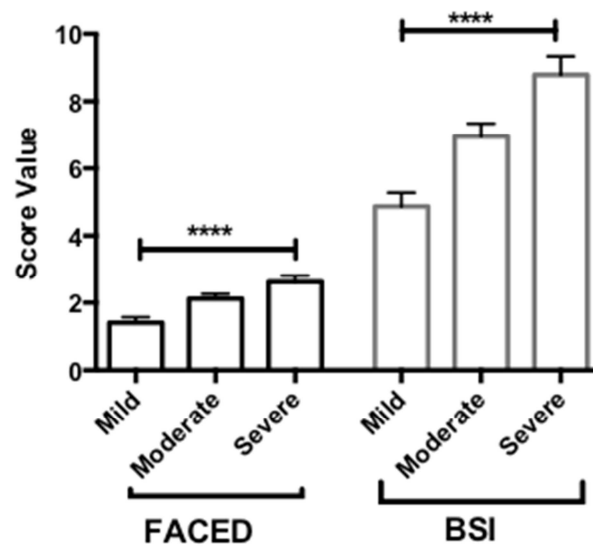
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e-Table 1. Bhalla Score

Category	0	1	2	3
Severity of bronchiectasis	Absent	Mild (lumen just > diameter of adjacent vessel)	Moderate (lumen 2-3 times > diameter of adjacent vessel)	Severe (lumen >3 times diameter of adjacent vessel)
Peribronchial thickening	Absent	Mild (wall thickness = diameter of adjacent vessel)	Moderate (wall thickness ≤ 2 times diameter of adjacent vessel)	Severe (wall thickness > 2 times diameter of adjacent vessel)
No. of bronchopulmonary segments involved	Absent	1-5	6-9	
Extent of mucus plugging	Absent	1-5	6-9	
Sacculations or abscesses	Absent	1-5	6-9	
Generations of bronchial divisions involved	Absent	Up to 4 th generation	Up to 5 th generation	> 6 th generation
No. of bullae	Absent	Unilateral; not >4	Bilateral; not >4	>4
No. of bronchopulmonary segments with emphysema	Absent	1-5	>5	
Collapse or consolidation	Absent	Subsegmental	Segmental or lobar	